

Amendments to the Claims

Amendments to the claims are reflected in the following listing of claims, which replaces and supercedes all previous listings of claims:

1. (Currently amended) An isolated peptide ~~comprising~~ with an amino acid sequence consisting of 8-100 amino acids, ~~comprising~~

wherein the peptide binds to VEGFR-3, and

wherein the amino acid sequence includes eight amino acids satisfying the formula: $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are amino acid residues, ~~wherein said peptide binds to VEGFR3,~~ wherein

the amino acid residue at X_1 is a glycine residue or a conservative substitution thereof;

the amino acid residue at X_2 is a tyrosine residue or a conservative substitution thereof;

the amino acid residue at X_3 is a tryptophan residue or a conservative substitution thereof;

the amino acid residue at X_4 is a leucine residue or a conservative substitution thereof;

the amino acid residue at X_5 is a threonine residue or a conservative substitution thereof;

the amino acid residue at X_6 is an isoleucine residue or a conservative substitution thereof;

the amino acid residue at X_7 is a tryptophan residue or a conservative substitution thereof;
and

the amino acid residue at X_8 is a glycine residue or a conservative substitution thereof,

and wherein the peptide comprises no more than 3 conservative amino acid substitutions introduced at positions $X_1 - X_8$.

2. (Previously Presented) The isolated peptide according to claim 1, further comprising amino- and carboxy-terminal cysteine residues.

3. (Currently amended) The isolated peptide according to claim 1, ~~comprising an~~ wherein the amino acid sequence of satisfies the formula: CX₁X₂X₃X₄X₅X₆X₇X₈C (SEQ ID NO: 33).

4. (Currently amended) The isolated peptide according claim 1, wherein:
the conservative substitution at position X₁ is selected from the group consisting of isoleucine, valine, leucine, alanine, cysteine, phenylalanine, proline, tryptophan, tyrosine, norleucine and methionine;

wherein the conservative substitution at position X₂ is selected from the group consisting of isoleucine, valine, leucine, alanine, cysteine, glycine, phenylalanine, proline, tryptophan, norleucine and methionine;

wherein the conservative substitution at position X₃ is selected from the group consisting of isoleucine, valine, leucine, alanine, cysteine, glycine, phenylalanine, proline, tyrosine, norleucine and methionine;

wherein the conservative substitution at position X₄ is selected from the group consisting of isoleucine, valine, alanine, cysteine, glycine, phenylalanine, proline, tryptophan, tyrosine, norleucine and methionine;

wherein the conservative substitution at position X₅ is selected from the group consisting of asparagine, glutamine, and serine;

wherein the conservative substitution at position X₆ is selected from the group consisting of valine, leucine, alanine, cysteine, glycine, phenylalanine, proline, tryptophan, tyrosine, norleucine or methionine;

wherein the conservative substitution at position X₇ is selected from the group consisting of isoleucine, valine, leucine, alanine, cysteine, glycine, phenylalanine, proline, tyrosine, norleucine and methionine; and

wherein the conservative substitution at position X₈ is selected from the group consisting of isoleucine, valine, leucine, alanine, cysteine, phenylalanine, proline, tryptophan, tyrosine, norleucine and methionine.

5. – 11. (Cancelled)

12. (Previously Presented) The isolated peptide according to claim 1, comprising the sequence $Y_1GYWLTIWGY_2$ (SEQ ID NO: 34), wherein Y_1 and Y_2 are amino acids.

13. (Original) The isolated peptide of claim 1, wherein said peptide comprises the sequence CGYWLTIWGC (SEQ ID NO: 35).

Claims 14-20. (Canceled)

21. (Currently amended) An isolated peptide ~~comprising~~ with an amino acid sequence consisting of 7-100 amino acids

wherein ~~comprising~~ the amino acid sequence includes amino acids satisfying the formula $GYWX_1X_2X_3W$ (SEQ ID NO: 67), wherein X_1 , X_2 , and X_3 comprise amino acids, and

wherein the peptide binds VEGFR-3.

22. (Currently amended) The isolated peptide according to claim 21, ~~comprising~~ wherein the amino acid sequence satisfies the formula $GYWX_1X_2X_3WX_4$ (SEQ ID NO: 68), wherein X_4 comprises an amino acid.

23. (Previously Presented) The isolated peptide according to claim 21 or 22, further comprising amino- and carboxy-terminal cysteine residues.

24. (Previously Presented) An isolated peptide according to any one of claims 1 or 21, wherein said peptide further comprises an intramolecular bond between amino acid residues to form a cyclic peptide.

25. (Previously Presented) The isolated peptide according to claim 24, wherein the peptide comprises amino- and carboxy-terminal cysteines, and the intramolecular bond comprises a disulfide bond between the cysteines.

26. (Previously Presented) The isolated peptide according to any one of claims 1 or 21, wherein said peptide inhibits Vascular Endothelial Growth Factor C (VEGF-C) binding to VEGFR-3.

27. (Currently amended) The isolated peptide according to any one of claims 1 or 21, further comprising a cytotoxic agent, or a label attached to the peptide.

28. (Previously Presented) The peptide according to claim 27, wherein the cytotoxic agent comprises a radioisotope.

29. (Previously Presented) The peptide according to claim 27, wherein the cytotoxic agent comprises an anti-neoplastic pro-drug.

30. (Previously Presented) A chimeric protein comprising a therapeutic protein amino acid sequence attached to the amino acid sequence of a peptide according to any one of claims 1 or 21.

31. (Previously Presented) The chimeric protein according to claim 30, wherein the therapeutic protein comprises a tumor necrosis factor.

32. (Previously Presented) The peptide according to any one of claims 1 or 21 attached to an antibody or fragment thereof.

33. (Previously Presented) The isolated peptide of any of claims 1 or 21, wherein said peptide further comprises a modification to increase the circulating *in-vivo* half-life of the peptide in a mammal.

34. (Previously Presented) A peptide dimer comprising first and second peptide monomers, wherein at least one of the peptide monomers comprises a peptide according to any one of claims 1 or 21, and wherein the dimer binds to VEGFR-3.

35. (Previously Presented) A peptide dimer comprising first and second peptide monomers that comprise peptides according to any one of claims 1 or 21.

36. (Previously Presented) The peptide dimer according to claim 35, wherein the first and second monomers comprise the same peptide.

37. (Previously Presented) The isolated peptide according to any one of claims 1 or 21, wherein said peptide further binds to at least one growth factor receptor selected from the group consisting of VEGFR-1, VEGFR-2 and neuropilin-1 (NP-1) and neuropilin-2 (NP-2).

38. (Previously Presented) A composition comprising an isolated peptide according to any one of claims 1 or 21 in a pharmaceutically acceptable carrier.

39. (Withdrawn) A method of inhibiting the proliferation of a cell comprising contacting a cell that expresses VEGFR-3 with a peptide according to any one of claims 1 or 21 in an amount effective to inhibit the proliferation of said cell.

40. (Withdrawn) The method of claim 39, wherein said cell is an endothelial cell or endothelial progenitor cell.

41. (Withdrawn) The method of claim 39, wherein said cell is a lymphatic endothelial cell.

42. (Withdrawn) The method of claim 39, wherein said cell is a mammalian hematopoietic progenitor cell.

43. (Withdrawn) The method of claim 39, wherein said contacting comprises contacting said cell with a composition comprising said peptide in a pharmaceutically acceptable carrier.

44. (Withdrawn) A method for inhibiting proliferation of a cell that expresses VEGFR-3, comprising a step of contacting the cell with a nucleic acid comprising a nucleotide sequence encoding the peptide of claims 1 or 21 and further comprising a promoter active in said cell, wherein said promoter is operably linked to the nucleotide sequence encoding said peptide, under conditions permitting the uptake of said nucleic acid and expression of said peptide by said cell in an amount effective to inhibit the proliferation of said cell.

45. (Withdrawn) The method of claim 44, wherein said nucleic acid is encapsulated in a liposome.

46. (Withdrawn) The method of claim 44, wherein said nucleic acid is a viral vector selected from the group consisting of retrovirus, adenovirus, adeno-associated virus, vaccinia virus and herpesvirus.

47. (Withdrawn) The method of claim 39, wherein said cell is contacted *in vitro*.

48. (Withdrawn) The method of claim 39, wherein said cell is contacted *in vivo*.

49. (Withdrawn) A method of treating a mammalian subject to modulate the growth in said subject of cells that express VEGFR-3, comprising administering to the mammalian subject a composition comprising a peptide according to any one of claims 1 or 21.

50. (Withdrawn) The method according to claim 49, wherein the mammalian subject has been diagnosed with a disease characterized by proliferation of endothelial cells that express VEGFR-3.

51. (Withdrawn) The method according to claim 50, wherein the disease comprises a tumor characterized by blood vessel or lymphatic vessel neovascularization, and wherein the neovascularization comprises endothelial cells that express VEGFR-3.

52. (Withdrawn) The method according to claim 50, wherein the disease comprises a cancer wherein the cancer cells express VEGFR-3.

53. (Withdrawn) The method according to claim 50, wherein the disease comprises a cancer wherein the cancer cells express a VEGFR-3 ligand selected from VEGF-C and VEGF-D.

54. (Withdrawn) A method of inhibiting metastatic spread of a cancer in a mammalian subject comprising administering to a mammalian subject suspected of having cancer a peptide according to any one of claims 1 or 21, in an amount effective to inhibit metastatic spread of said cancer.

55. (Withdrawn) A method for treating cancer comprising administering to a mammalian subject diagnosed with a cancer a composition comprising a peptide according to any one of claims 1 or 21, in an amount effective to reduce growth or neoplastic spread of the cancer.

56. (Withdrawn) The method according to claim 49, wherein the subject is a human.
57. (Withdrawn) The method according to claim 55, wherein said peptide inhibits at least one of angiogenesis and lymphangiogenesis near the cancer in said subject.
58. (Withdrawn) The method according to claim 55, wherein said cancer is breast cancer.
59. (Withdrawn) A method of treating a mammalian subject having a disease characterized by proliferation of cells that express at least one of VEGFR-3, VEGF-C, and VEGF-D, comprising a step of administering to the subject a nucleic acid comprising a nucleotide sequence encoding a peptide according to any one of claims 1 or 21 and further comprising a promoter, wherein said promoter is operably linked to the nucleotide sequence encoding said peptide.
60. (Withdrawn) The method according to claim 49, further comprising a step of administering to the subject a second cancer therapeutic agent.
61. (Withdrawn) The method of claim 60, wherein said second cancer therapeutic agent comprises a chemotherapeutic agent, a radioactive agent, a nucleic acid encoding a cancer therapeutic agent and anti-lymphangiogenic agent or an anti-angiogenic agent.
62. (Withdrawn) The method according to claim 39, wherein the subject has been diagnosed with an operable tumor, and wherein the administering step is performed before, during, or after the tumor is resected.
63. (Withdrawn) A method according to claim 49, wherein the subject has a cancer of a tissue, organ, or cell selected from the group consisting of brain, lung, liver, spleen, kidney,

lymph node, small intestine, blood cells, pancreas, colon, stomach, breast, endometrium, prostate, testicle, ovary, skin, head and neck, esophagus, bone marrow and blood.

64. (Withdrawn) A method of treating a pathology characterized by VEGFR-3 binding to a natural ligand that binds VEGFR-3, comprising the step of administering to an individual in need thereof a peptide according to any one of claims 1 or 21.

65. (Withdrawn) A method of screening a biological sample for VEGFR-3, comprising steps of:

- a) contacting a biological sample suspected of containing VEGFR-3 protein with a composition comprising a peptide according to any one of claims 1 or 21; and
- b) determining the binding of said peptide with said receptor.

66. (Withdrawn) The method according to claim 65, wherein the peptide comprises a detectable label, and the determining step comprises detecting the presence of the label bound to the biological sample.

67. (Withdrawn) The method according to claim 65, wherein the biological sample comprises mammalian cells, and the determining step comprising determining the presence or quantity of peptide bound to the cells.

68. (Withdrawn) A method of imaging cells that express VEGFR-3 in a tissue suspected of containing cells that express VEGFR-3 comprising:

- a) contacting the tissue with a composition comprising a peptide of any one of claims 1 or 21; and
- b) imaging cells that express VEGFR-3 in said tissue by detecting said peptide bound to cell in said tissue.

69. (Withdrawn) The method of claim 68, wherein said peptide comprises a detectable label, and wherein the imaging step comprises detecting the label in the tissue.

70. (Withdrawn) The method of claim 69, wherein said tissue is human tissue.

71. (Withdrawn) The method of claim 70, wherein said tissue is neoplastic tissue.

72. (Withdrawn) A method of screening for neovascularization in a tumor, comprising steps of:

contacting a tissue suspected of containing a tumor with a peptide according to any one of claims 1 or 21; and

detecting binding of the peptide in the tissue, wherein binding of the peptide to the tissue correlates with the presence of neovascularization in the tissue.

73. (Withdrawn) The method according to claim 72, wherein the peptide comprises a label, and the detecting step comprises measuring the quantity and/or distribution of the label.

74. (Withdrawn) The method of diagnosing a cancer, comprising screening for neovascularization according to claim 73, wherein increased quantity and/or distribution of the label correlates with increased neovascularization and increased aggressiveness of the tumor.

75. (New) The peptide of claim 27 wherein the label is selected from the group consisting of a radionuclide, a dye, an enzyme, and an enzyme substrate.